REMARKS

By the foregoing amendments, claims 13 and 14 have been amended. Support for the amendment to claim 13 can be found in the specification at page 8, Example 3. Support for new claim 18 can be found in original claim 14. Claims 1-12 are withdrawn. Claims 13-18 are under examination.

Information Disclosure Statement

Applicants acknowledge with thanks the Examiner's comments with respect to the Information Disclosure Statement submitted on September 3, 2008, and the new copy of Form 1449 with Examiner annotations. The following table sets forth the correspondence between the European patents that the Examiner has lined out, and corresponding U.S. patents and applications, all of which are of record in the subject case. Therefore, the following U.S. patents are not resubmitted in the IDS submitted herewith.

Foreign Citation	Date	Country	US relevance
037231	01/28/1987	EP	US4350704; US4425355
049658	06/13/1984	EP	US4508729
0308340	03/13/1991	EP	US4902817
0308341	12/12/1990	EP	US4914214
0308339	05/06/1992	EP	US4935525, US4954640
1338951	08/27/2003	EP	US7157484
1362845	11/19/2003	EP	US2006252958

Applicants note that the prior submission of Form 1449 with the September 3, 2008 IDS contained a typographical error for the U.S. patent corresponding to EP 1362845. For this reason, Applicants resubmit the correct U.S. patent publication no., US 2006/0252958 in the IDS submitted herewith.

Applicants also note that the prior submission of EP1323729 in the September 3, 2008 IDS is now substituted with the English abstract of WO 04/083237 in the IDS submitted herewith.

The Rejection under 35 USC § 112

Claims 16-17 are rejected under Section 112, first paragraph, as non-enabled for indipamide "hydrates." Vippagunta et al., Advanced Drug Delivery Reviews 48(2001) 3:26, is cited for its teaching that predicting the formation of hydrates of a compound, and the structure of the crystal lattice of the hydrate, is not predictable.

Applicants respectfully point out that hydrate of indipamide was known in the art before the filing date of the subject application, as evidenced by The Merck Index (2001) definition provided in the IDS provided herewith. Applicants are not claiming a particular hydrate structure so that it not seen how the teachings of Vippagunta et al. relating to predictability of hydrate structure are relevant. Applicants request withdrawal of the subject rejection.

Claim 14 is rejected under Section 112, second paragraph, as indefinite for recitation of "preferably." By the foregoing amendment, "preferably 1 to 0.50-0.83" has been deleted from claim 14. Further, this deleted language has been moved into new claim 18.

Claims 13-17 are rejected under Section, 112, second paragraph as indefinite for recitation of "low moisture contents" and/or "substantially anhydrous." By the foregoing amendment to claim 13, both of these phrases have been deleted from claim 13. It is believed that this rejection is now fully addressed and withdrawal is respectfully requested.

The Rejection under 35 USC § 103

Claims 13-14 are rejected over Guez et al, WO 99/25374 (US 6,653,336) and Eyjolfsson, WO 03/059388. Guez et al. teach ACE inhibitors including perindopril in combination with microcrystalline cellulose. Guez et al. do not teach carbonates. Eyjolfsson et al. teach carbonates in combination with ACE inhibitors. Signet sheets teach AVICEL PH-101 which has low moisture content.

It is argued by the Examiner that the claimed limitation of DKP content at 3 weeks storage at 50°C in a closed container, is intrinsic to a composition with perindopril, at least one of microcrystalline cellulose and anhydrous lactose, at least one inorganic carbonate, and optionally other components. As a result, when the composition

limitations are met, the properties would intrinsically be met. However, Applicants note that none of the cited references teach anhydrous lactose.

By the foregoing amendments, Applicants have amended claim 13 to recite that "anhydrous lactose" is a required component of the composition. Where the cited prior art fails to teach a recited element in the claim, *prima facie* obviousness is not established (*In re Boe*, 184 USPQ 38 (CCPA 1974); *In re Royka*, 180 USPQ 580 (CCPA 1974)). Withdrawal of the subject rejection is respectfully requested.

Claims 15-17 are rejected under Section 103(a) over Guez et al., Eyjolfsson as applied to claims 13 and 14 as discussed above, in view of www.signetchem.com, and further in view of Cooper et al., US Pat. Publication 2003/0137067. www.signetchem.com teaches the commercial availability in 2002 of microcrystalline celluloses with different properties, size and forms. However, it does not teach anhydrous lactose. Cooper et al. is cited for its teaching regarding polycosanol nanoparticulates which might be used to obtain control-release forms. Cooper et al. teach polycosanols as active agents. Polycosanols are a complex mixture of concentrated n-alkyl alcohols derived from sugar cane and the wax of honey bees ([0008]). Cooper et al. mention the possibility that other active compounds might be included such as ACE inhibitors ([0077] - [0078]). However, Cooper et al. do not mention perindopril. We further note that Cooper et al. describe in its section on "Other Active Agents" ([0077] – [0085]), thousands of compounds that are not even the main focus of the reference, without there being any indication that would lead the skilled artisan in the direction of including ACE inhibitors (or perindopril), making the combination of Cooper et al. with the Guez et al. and Eyjolfsson untenable. Applicants respectfully request withdrawal of the subject rejection.

Claims 13-14 are rejected under Section 103(a) as obvious over Patel et al., U.S. Publication No. 2005/0142196. Patel et al. teach a combination of an ACE inhibitor (e.g., perindopril), a carbonate and hydroxypropyl cellulose in a wet granulation procedure to produce a pharmaceutical composition. Although the possibility of a dry granulation procedure is mentioned, it is clearly stated that wet granulation is preferred ([0044]).

The wet granulation step is followed by drying in Patel et al., but as described in the subject specification (page 5, 6th paragraph), a wet granulation process must be completely avoided in order to avoid degradation reactions associated with the presence of water, and to achieve the low level moistures recited in subject claim 13.

The hydroxypropyl cellulose of Patel et al. is partially substituted poly(hydroxypropyl) ether of cellulose having a molecular weight of 50,000 to 1,250,000, preferably KLUCEL™ of at least 80,000 MW ([0016] – [0022]). Also preferred is low-substituted hydroxypropyl cellulose under the trade designation L-HPC Grade LH-21 and LH-11 ([0031]). These have a particle size greater than 25 μm (page 2, [0024] – [0030]). The foregoing molecular weights for microcrystalline cellulose in Patel et al. place it outside the definition of "microcrystalline cellulose" as provided by the World Health Organization, Food and Agriculture Organization (copy provided in IDS submitted herewith).

The stabilized pharmaceutical compositions of Patel et al. may contain one or more excipients but only if they do not deleteriously affect the stability of the pharmaceutical compositions ([0033] – [0034]). These include fillers such as microcrystalline cellulose. Applicants point out that the microcrystalline cellulose is optional and is not added for stabilization purposes.

Patel et al. specifically teach away from the addition of a saccharide, especially lactose ([0034]). Patel et al. do not teach anhydrous lactose.

It is therefore submitted that Patel et al. do not establish *prima facie* obviousness of subject claim 13.

The Examiner has argued:

> . . . It is noted that the limitation [in claim 13] of the DKP content at 3 weeks storage at 50°C in a closed container as written, would be intrinsic to a composition with perindopril, at least one of microcrystalline cellulose and anhydrous lactose, at least one inorganic carbonate, and optionally other components. As a result when the composition limitations are met, the properties would be intrinsically be met.

Applicants respectfully point out that the composition limitations have not been met because Patel et al. teach away from the inclusion of lactose, and do not teach anhydrous lactose at all. Further, Patel et al. would discourage the skilled artisan from combining

any reference that taught the inclusion of lactose. Where the cited prior art fails to teach a recited element in the claim, obviousness is not established (*In re Boe*, *supra*; *In re Royka*, *supra*). For these reasons, Patel et al. cannot be said to establish *prima facie* obviousness. Withdrawal of the rejection is respectfully requested.

Claim 15 is rejected under Section 103(a) over Patel et al as applied to claims 13-14 in view of www.signetchem.com. www.signetchem.com is cited for its teaching of low moisture content microcrystalline cellulose. However, www.signetchem.com does not describe anhydrous lactose and does not therefore supply the deficiencies of Patel et al. Claim 15 is therefore respectfully submitted to be non-obvious over the cited references.

Claim 16 is rejected as obvious under Section 103(a) over Patel et al in view of www.signetchem.com as applied to claim 15, in view of Guez et al. Applicants again respectfully point out that while Guez et al. may describe indipamide, they do not describe anhydrous lactose.

Claim 17 is rejected as obvious under Section 103(a) over Patel et al., www.signetchem.com, Guez et al., as applied to claim 15, further in view of Cooper et al. The Examiner argues that Patel et al. teach that the hydroxypropyl cellulose particle sizes are 40 – 50 μm (paragraph 23-31). Applicants have noted above that the molecular weights for microcrystalline cellulose in Patel et al. place it outside the definition of "microcrystalline cellulose" as provided by the World Health Organization, Food and Agriculture Organization.

The Examiner also argues that Cooper et al. indicates that its active ingredients include antihypertensive agents. Applicants respectfully point out that the active ingredients in Cooper et al. are polycosanols which are n-alkyl alcohols; antihypertensives are identified only as one potential class of hundreds or thousands of optional "Other Active Agents" that might be included ([0077] – [0085]). Further, no direction is given to the skilled artisan in Cooper et al. to direct the skilled artisan to include ACE inhibitors, and perindopril is not even mentioned by Cooper et al. There is no reason to combine Cooper et al. with the other cited references.

For the foregoing reasons, it is respectfully requested that the Section 103(a) rejections be withdrawn.

Closing Remarks

It is believed that the foregoing amendments and remarks bring the subject case into condition for allowance and notification of same is respectfully requested. If it is believed that a phone conference would expedite prosecution, the Examiner is invited to phone the undersigned.

Submitted herewith is a Petition for Extension of Time for one month with an authorization to charge the requisite fee to Deposit Account No. 19-5117. It is believed that no other fee is due with this submission. If this is in error, please charge any necessary fee to Deposit Account No. 19-5117.

Respectfully submitted,

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